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(54) Title: ODOR-MASKED AND STABILIZED COMPOSITIONS FOR TREATING KERATINOUS TISSUE, SKIN CONDITIONS, AND PROMOTING WOUND HEALING

(57) Abstract

This invention relates to odor-masked and storage stable compositions comprising film-forming proteins containing reducing agents and optionally at least one component selected from the following: reactive zinc salts, cationic polymers and cationic or nonionic surfactants. The present invention also relates to these compositions containing oxidizing agents and/or antioxidants and methods of use. The therapeutic compositions and methods of the present invention are particularly effective in promoting wound healing, and in inhibiting certain skin disorders, including eczema and seborrhea, scleroderma, hang nails, wrinkling and acne, including acne scarring. The therapeutic compositions and methods of the present invention have also shown enhanced effect as veterinary tools in reducing the debilitation associated with certain skin conditions in mammals including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitus ulcers and canine cutaneous granulomas ("lick" granuloma). The compositions of the present invention are also useful for conditioning horny keratinous tissue of mammals such as human hair and nails, and the hooves and fur of animals to improve their strength and appearance. In addition, these compositions are useful for promoting hair and nail growth.

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ODOR-MASKED AND STABILIZED COMPOSITIONS FOR TREATING KERATINOUS TISSUE, SKIN CONDITIONS, AND PROMOTING WOUND HEALING

SUMMARY OF THE INVENTION

This invention relates to novel compositions using film forming protein ingredients and includes reducing agents and optionally at least one of the following: reactive zinc salts, cationic polymers and/or cationic or nonionic surfactants. In addition, oxidizing agents and/or antioxidants are optionally included. The compositions of the present invention are particularly effective in promoting wound healing, the healing of abrasions and pressure sores, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, and in inhibiting certain skin disorders and treating abnormal conditions of the skin, including eczema and seborrhea, dandruff, psoriasis and other rash-like indications, scleroderma and acne. The compositions of the present invention further may be used to reduce scarring associated with severe forms of acne or wounds and to ameliorate wrinkling in skin due to exposure to the sun's rays or to aging. The therapeutic methods of the present invention are effective as veterinary tools in reducing the debilitation associated with certain skin conditions in mammals including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitis ulcers, and canine cutaneous granulomas ("lick" granuloma). The compositions of the present invention are also useful as cosmetic agents for conditioning horny keratinous tissue of mammals such as human hair and nails and the hooves and fur of animals to improve their strength and appearance. In addition, these compositions are useful for promoting hair and nail growth and for stabilizing the loss of hair in mammals, including humans.

It has now been discovered that compositions of the present invention which include film-forming protein compositions, reducing agents and optionally sufficient quantities of at least one or more of the following components: zinc salts, cationic polymers and cationic or non-ionic surfactants and also optionally include oxidizing agents and/or anti-oxidant compositions exhibit surprising activity for treating wounds, pyoderma, sebborhea, psoriasis, acne, miscellaneous rashes,

defined percentages of thioglycollic acid, ammonium hydroxide, glycerine, citric acid, hydrogen peroxide, gelatin, a lower alkanol, and a solvent such as acetone or diethyl ether. Several examples of wound healing are provided in the specification.

United States Patent 4,195,095 describes the use of certain formulations comprising thioglycollic acid for use in the treatment of fatty cysts, dandruff, scleroderma and other dermatological disorders, including acne vulgaris. Exemplary compositions comprise thioglycollic acid, hexachlorophene, sodium hydroxide, water and other ingredients, including bulking or gelling polymers and preservatives, among others.

U.S. Patent 3,842,848 describes a method of bonding especially prepared hydrolyzed peptide products of keratinaceous materials to human hair. The process is effected by conducting the reducing step of permanent waving in the presence of the peptide products and, thereafter, in a second step, oxidizing.

U.S. Patent No. 4,711,780 describes a medication for treating surface epithelium comprising ascorbic acid, a zinc salt a sulfur amino acid and optionally a mucopolysaccharide and/or a polysaccharide. Compositions of this patent are described as being useful for treating a number of infections and conditions, including wound healing.

G.B. Patent No. 2,160,419 describes a process for treating and improving the condition of keratinous tissue comprising no fewer than three steps: contacting the hair, skin or nails with a reducing composition, rinsing the treated tissue with water, contacting the rinsed tissue with an aqueous keratin protein hydrolysate and finally contacting the tissue with a neutralising composition containing an oxidizing agent.

Compositions which contain film-forming protein (preferably an activated thiol-containing film-forming protein) and a reducing agent in the absence of the sulfur stabilizing components of the present invention, although highly efficacious, tend to develop a pungent, malodor which in certain compositions may be quite unpleasant. In certain instances, such compositions, because of this malodor, may reduce the frequency with which an individual applies the composition.

It is therefore one object of the present invention to provide novel compositions and/or methods for treating

BRIEF DESCRIPTION OF THE INVENTION

The therapeutic compositions and methods of the present invention are useful for treating keratinous and related conditions, including wounds, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, seborrhea, psoriasis, dandruff, allergic skin reactions, acne, itching, callouses, corns, burns, abrasions, wrinkles, miscellaneous rashes, non-specific dermatitis and certain veterinary conditions including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitis ulcers, and canine cutaneous granuloma ("lick" granuloma). In addition, the compositions and methods of the present invention may also be used to improve the strength, condition and appearance of hair, skin and nails, including split and cracked hair, nails and hooves, and for promoting the growth of hair and nails and preventing hair loss.

In using the present invention a composition comprising an activated protein, a compatible reducing agent, and optionally at least one of the following components: a reactive zinc salt, a cationic polymer and a surfactant selected from the group consisting of cationic and nonionic surfactants is contacted with an area of keratinous tissue affected with one of the above conditions. Further optionally, an oxidizing agent and/or an antioxidant may be included in the formulations of the present invention. The therapeutic compositions and methods of the present invention exhibit activity against non-healing skin conditions, especially canine cutaneous granulomas ("lick" granuloma) and equine exuberant granuloma ("proud flesh"). It is a particularly surprising result that certain compositions of the present invention are active in a broad range of applications without exhibiting the malodor associated with non-stabilized compositions or a substantial reduction in activity. Furthermore, the compositions of the present invention do not exhibit substantial "puckering" of packaging caused by compositions which do not contain at least one of the following: a reactive zinc salt, cationic polymer and cationic or nonionic surfactant.

Compositions useful in the therapeutic methods of the present invention include compositions having a pH of from about 3 to about 10, preferably a pH of about 4 to about 9. The pH of the composition depends upon the specific applica-

protein and the keratinous tissue. The time that the reducing agent is in contact with the keratinous tissue is also important; the longer the keratinous tissue is in contact with the reducing agent, the greater will be the likelihood of protein-keratinous tissue covalent bond formation.

The compositions of the present invention are preferably utilized at ambient temperatures, i.e., about 20°C to about 35°C; however, higher temperatures may be used, especially for treating the hair and nails of animals, including humans. Obviously, when treating a wound, especially a burn, treatment is kept to a lower temperature to avoid exacerbating the wound condition. Where the application of heat is viewed as advantageous, treating the keratinous substrate at higher temperatures is recommended. The keratinous tissue (hair and nails) may be treated over a period of time ranging from about 5 minutes to about 6 hours. The keratinous tissue may be treated acutely or chronically, with or without a dressing as needed. In certain embodiments, compositions useful in practicing the therapeutic methods of the present invention may be formulated with sustained or controlled release polymers to produce formulations capable of delivering active agent for extended periods of time. Reaction is effected by bringing the compositions of the present invention into contact with the keratinous substrate to be treated and allowing the treated tissue to dry. The time of contact may be varied at will.

In addition to the film-forming protein, compositions of the present invention also comprise at least one reducing agent, preferably a pharmaceutically compatible reducing agent. The reducing agent is preferably used in an amount sufficient to reduce the keratinous substrate to promote covalent binding of the film-forming protein. Although any reducing agent which is capable of producing free thiol groups from the disulfide bonds of cystine may be used in embodiments of the present invention, preferred reducing agents include pharmaceutically compatible thiol-containing reducing agents.

In addition to film-forming protein and reducing agent, the compositions preferably comprise at least one agent selected from among the following: reactive zinc salts, cationic polymers and surfactants selected from cationic and nonionic surfactants. When reactive zinc salts are used, they comprise a concentration effective for producing an odor-

the effectiveness of cationic polymers of the present invention to stabilize the compositions of the present invention. It is also believed that the zinc and cationic polymers or cationic and nonionic surfactants may complex with the thiol containing reducing agents and/or the proteins to stabilize these components from breakdown into malodorous side products.

Representative cationic polymers may contain nitrogen, phosphorous and sulfur cationic groups or mixtures of these cationic groups. Virtually any polymer containing cationic groups may be used in compositions of the present invention. Cationic polymers containing nitrogen and particularly quaternary ammonium groups are especially preferred.

It is preferred that the cationic polymers of the present invention are water soluble and contain quaternary-ammonium groups. Such polymers may be selected from among the quaternary nitrogen-containing cellulosic ethers, quaternary nitrogen-containing polysaccharides, graft copolymers of cellulose ethers and dialkyl diallyl ammonium halide polymers, copolymers of vinyl pyrrolidone and quaternized dialkylaminoalkyl methacrylate, copolymers of acrylamide and quaternized dialkyl amino dialkyl methacrylate as well as other polyquaternium polymers.

The cationic polymer is used in an amount effective to substantially reduce the malodor associated with the storage of thiol containing compositions, for example reducing agents and proteins which are included in the compositions of the present invention. In general, the cationic polymer used in the present invention comprises at least about 0.01 percent by weight to about 20 percent by weight, preferably about 0.025% to about 20% by weight and most preferably about 0.1% to about 5% by weight of the composition.

As stated hereinabove, the cationic polymer may be used alone or in combination with reactive zinc salts and/or surfactants. Where compositions are formulated using a cationic polymer in the presence of reactive zinc salts and/or pyrrolidone containing surfactants, the amount of cationic polymer, although generally falling within the weight ranges described hereinabove, may be reduced to accommodate the reactive zinc salt and/or surfactant chosen.

Compositions of the present invention may also contain at least one surfactant selected from among cationic and nonionic surfactants.

about 0.9% by weight and most preferably between about 0.35 and 0.7% by weight of the composition.

In addition to the above-described components, compositions of the present invention may be formulated with an oxidizing agent, an antioxidant or mixtures of an oxidizing agent and an antioxidant. In addition, other components may also be added to the compositions of the present invention with or without the incusion of zinc salts, cationic polymers or nonionic and cationic surfactants including at least one or more of the following: acids, bases, buffering agents, emulsifying agents or additional surfactants, thickeners, preservatives, bulking agents, organic solvents, coloring agents and perfume agents. It is to be recognized by those of ordinary skill in the art that the choice of additives is made to avoid interactions with the active components of compositions of the present invention.

In certain embodiments of the present invention, depending upon the anti-oxidant used the reaction may be facilitated by heat. By removing the antioxidant in this manner, oxidation to promote covalent disulfide formation by the oxygen in ambient air may be promoted. Certain embodiments of the present invention may employ non-volatile oxidizing agents which may promote oxidation after the volatile antioxidants evaporate from the formulations.

In general, compositions of the present invention comprise about 0.1% to about 25% by weight of a film-forming protein, preferably an activated protein component, about 1.0% to about 15% by weight of a compatible reducing agent, preferably at least one agent selected from among reactive zinc salts, cationic polymers and cationic and nonionic surfactants, and at least one component selected from the group consisting of oxidizing agents, antioxidants, water, acids, bases, buffering agents, emulsifying agents or surfactants, thickeners, preservatives, organic solvents, chelating agents, film-forming polymers, coloring agents and perfuming agents.

Preferred compositions for use in the method aspects of the present invention are formulated to enhance the formation of free mercaptide or thiol groups in a thiol containing protein and the keratinous tissue to maximize the probability that a free thiol in the protein and a free thiol in the keratinous tissue will interact to form a covalent disulfide bond. The inclusion of an oxidizing agent in the same for-

other applications.

Film-forming proteins used in compositions employed in the present invention are exemplified by a number of proteins. Preferred proteins are those containing sufficient cysteine, i.e., at least about 1 cysteine amino acid for every 200 amino acids in a peptide chain (approximately, at least about 0.5% by weight cysteine, preferably, at least about 1.0% by weight cysteine, and most preferably at least about 5% by weight cysteine) to covalently bind to the keratinous tissue of hair, skin and nails to produce a durable permanent bond to keratinous tissue. By permanent bond we mean that the protein is not easily washed or rubbed off from the keratinous tissue and becomes as permanent as normal hair and nails.

A large number of exemplary film-forming proteins may be used in the present invention including gelatin, collagen, mucin, salmine, and sturine. Preferred proteins include keratin, food proteins, for example, casein, alpha and beta-lactalbumin, seed proteins, for example, soybean proteins, linseed protein, cotton seed protein, corn protein and peanut protein, among others, hemoglobin, insulin, myosin, zein, ovalbumin, hemoglobin, trypsin, chymotrypsin, chymotrypsinogen, elastases, thrombins, plasminogen, fibrinogen/fibrin, lysozyme, papain, serum albumin, heat coagulable mucoproteins isolated from cartilage, bones and skin, gamma globulin blood proteins, and a number of the blood factor proteins, including, for example, factor VIII, XII, IXa and Xa, among others. Of course, proteins which contain large numbers of cysteinyl residues are preferred, because these proteins would form the greatest number of covalent bonds with the keratinous tissue and thus, produce the greatest durability. The most preferred film-forming proteins for use in the present invention are those which contain sufficient cysteine to covalently bind to the keratinous substrate being treated.

Particularly preferred proteins for use in the present invention include proteins containing high percentages by weight of cysteine, for example, ribonuclease T1, human serum albumin and gamma globulins. An especially preferred protein for use in the present invention is keratin, because of its particularly high cysteine content (about 12% to about 17% by weight of cysteine) and because it is found in those substrates which are conditioned. In compositions to be used to treat certain wounds, exemplary compositions utilize keratin

than 10% by weight of the protein and often as high as 15-17% by weight of the protein) which may be obtained by hydrolysis of skin, feathers, wool and hair. A particularly preferred keratin is Kerasol^{tm} from Croda Chemicals International, Chesire, England. The molecular weight of proteins useful in the present invention preferably varies between about 5,000 and 500,000 Daltons, and most preferably varies between about 120,000 and 130,000 Daltons.

Reducing agents which are useful in compositions of the present invention include sulfides, thiol-containing compositions including dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, thioalkanoic acid and mercaptocarboxylic acid analogues, for example, mercaptosuccinic acid, thiolactic acid and their pharmaceutically acceptable salts, among others, including thioglycollic acid and salts of thioglycollic acid. Preferred reducing agents for activating the protein are thioglycerol, cysteine, thiolactic acid and thioglycollic acid, and their pharmaceutically acceptable salts. Especially preferred reducing agents for use in the present invention include thioglycerol and salts of thioglycollic acid, especially ammonium thioglycollate. It is preferred that the reducing agent for activating the protein should be the same as the pharmaceutically compatible reducing agent which is used in the final formulation of the invention. The use of strong pharmaceutically incompatible reducing agents to activate the protein are less preferred and may make the use of the protein more difficult because the reducing agent may have to be removed from the activated protein before formulation.

In addition to a film-forming protein, compositions for use in the method of the present invention also contain a pharmaceutically compatible reducing agent in an amount equal to about 0.1 to about 15% by weight of the formulation. Preferred compositions contain about 0.5% to about 10% by weight, most preferably greater than about 1% by weight of a pharmaceutically compatible reducing agent. The amount of pharmaceutically compatible reducing agent varies according to the therapeutic or cosmetic use for which the compositions are intended, but generally falls within the range of about 0.1% to about 10% by weight. A pharmaceutically compatible reducing agent is an agent which reduces cystinyl disulfide linkages in keratinous tissue to produce free thiol or mercap-

contemplated for use in the present invention. Such cationic polymers may be selected from among synthetic, semi-synthetic and natural cationic polymers. The cationic polymers of the present invention may be selected from among polysaccharides, for example polycellulosic polymers, condensation polymers, polyamines, polyoxyalkylenes, polyalkyleneimines, homo and co-polymers of ethylenically unsaturated compounds, including poly(meth)acrylamides, poly(meth)acrylates, polyvinylpyrrollidones, diallyl dialkyl ammonium halides, as well as grafts or copolymers of such materials, among others, each of which contains cationic groups.

It is preferred that the cationic polymers of the present invention are water soluble and contain quaternary-ammonium groups. Exemplary preferred polymers may be selected from among the quaternary nitrogen-containing cellulosic ethers for example, JR-30M^{tm}, JR-125^{tm} and JR-400^{tm}, available from Amerchol Corp. New Jersey, USA, LR-400, LR-30M and SR-10, available from Union Carbide Corp., USA, quaternary nitrogen-containing polysaccharides, for example the Quatrisoft^{tm} polymers available from Union Carbide Corp., graft copolymers of cellulose ethers and dialkyl diallyl ammonium halide polymers, for example the Celquat^{tm} polymers, availabe from National Starch, New Jersey, USA, homo and copolymers of of dialkyl diallyl ammonium halide, for example the Merquat^{tm} polymers available from Calgon Corp., USA, copolymers of vinyl pyrrolidone and quaternized dialkylaminoalkyl methacrylate, for example, the Gafquat^{tm} polymers, available from GAF Corp., Linden, New Jersey USA, copolymers of acrylamide and quaternized dialkyl amino dialkyl methacrylate, for example, the Reten^{tm} polymers, available from Hercules, Inc., Wilmington, Del. USA as well as other polyquaternium polymers.

The cationic polymer is used in an amount effective to substantially reduce the malodor associated with the storage of thiol containing compositions, for example reducing agents and certain proteins which are included in the compositions of the present invention. In general, the cationic polymer is used in an amount comprising at least about 0.01 percent by weight to about 20 percent by weight, preferably about 0.025% to about 20% by weight and most preferably about 0.1% to about 5% by weight of the composition. Some cationic polymers may produce irritation when placed in proximity to the skin. Those of ordinary skill in the art will understand to adjust

templated by the present invention.

Compositions of the present invention may also contain at least one nonionic surfactant. Nonionic surfactants which are useful in the present invention include those surfactants which complex with mercaptides. Especially preferred nonionic surfactants for use in compositions of the present invention include, for example, those nonionic surfactants having cationic character, i.e., exist as cations in certain resonance forms which may complex with mercaptides and stabilize the compositions of the present invention from producing malodorous side products. Preferred nonionic surfactants for use in the present invention include alkanolamide surfactants, Amide 6560^{tm}, available from Emery Corp., Mauldin, South Carolina, USA, ethoxylated alkanolamides, for example, ethoxylated taloamine, Trymeen^{tm} surfactant, available from Emery Corp., South Carolina and pyrrolidone containing surfactants. In addition to the above, certain fatty alcohol nonionic surfactants such as for example seteth and steareth alcohols may also be included in compositions of the present invention.

Compositions of the present invention most preferably contain at least one pyrrolidone containing surfactant in which a hydrophobic group is attached to the nitrogen of the pyrrolidone ring. Although a number of hydrophobic groups on the nitrogen of the pyrrolidone ring may be employed, preferred hydrophobic groups include n-octyl, dodecyl and coco and tallow alkyl groups, most preferably n-octyl, attached to the nitrogen of the pyrrolidone ring in the surfactants LP-100^{tm}, LP-300^{tm}, LP-800^{tm}, and LP-940^{tm}, available from GAF Corp., Linden, New Jersey USA. Generally, the compositions of the present invention contain about 0.05 to about 5% by weight of a pyrrolidone containing surfactant.

The presence of reactive zinc salts, cationic polymers and/or cationic and nonionic surfactants are used in amounts alone or in combination effective to stabilize the compositions of the present invention. By stabilizing the compositions of the present invention, the compositions do not exhibit appreciable malodor, precipitation or "puckering" of containers caused by reaction of the formulations with gasses present in the container.

In certain aspects of the present invention, ethylenediaminetetraacetic acid (EDTA), for example Hampene 100^{tm}, available from Lowenstein, Inc., Brooklyn, New York,

often advantageous to include an oxidizing agent, because the oxidizing agent may promote the polymerization of certain keratin molecules in situ, a condition which is advantageous for promoting the film-forming characteristics of certain thiol containing proteins.

Compositions of the present invention may also include an antioxidant instead of, or in addition to, an oxidizing agent in an amount equal to about 0.01 to about 2.0% by weight of the composition. In compositions comprising an antioxidant, the antioxidant is included to promote the storage stability of the formulations. Exemplary antioxidants may include alpha-tocopherol, hydroxyquinone, unipherol, tocopherol ascorbate, lecithin, chlorophyll, ascorbylpalmitate, linseed oil, tongue oil, other natural antioxidants such as the steam distillation extract of rosemary as disclosed in U.S. Patent No. 4,450,097, thiazoline carboxylate, dihydroquinolines, methyl gallate, propyl gallate, alkylaryl and diarylamines.

Certain chelating agents, for example, EDTA, may be employed to enhance the antioxidant effect of the above agents. It has also been found advantageous to add EDTA to the formulations containing a reactive zinc salt, as described hereinabove. The chelating agent may function to chelate any dissolved metals which may be responsible for the in situ generation of oxygen. Generally, the chelating agent comprises between about 0.05 to about 2.0% by weight of the formulation, preferably about 0.2 and about 0.9% by weight and most preferably about 0.35 to about 0.7% by weight of the composition.

In preferred embodiments of the present invention, when an oxidizing agent is not included in the formulations utilized, about 0.01% to about 2.0% of antioxidant is included in the formulations. Without the additional oxidizing agent, the antioxidant is included in compositions of the present invention to prevent atmospheric oxygen or oxygen dissolved in the solution from deactivating the protein or the reducing agent during storage. In compositions in which oxidizing agents are employed to promote the oxidation of free thiols or mercaptides to covalent disulfide bonds, the oxidizing agent comprises about 0.01% to about 4.0% by weight of an oxidizing agent and the antioxidant comprises about 0.01% to about 4.0% of the formulation.

0.75% by weight. The pH of the formulation may be a factor in determining its stability and in maintaining the activity of certain components in the formulation, especially the activated protein and the compatible reducing agent. Thus, a buffering agent may be included within the formulation to maintain the pH at a relatively constant level over time.

To add homogeneity to and promote the solubility of the formulation, certain organic solvents may be included. Among the solvents that may be useful in certain embodiments of the present formulation are water soluble polar organic solvents, for example alkanols such as methanol, ethanol, propanol, butanol and carbonyl containing solvents for example acetone, butanone and the like, among others. Additional solvents include ethers and amines, for example diethyl or dipropyl ether and trimethyl or triethyl amine. Trimethylamine and triethylamine may also be added as bases.

The solvent added to the formulation may enhance the solubility of certain components. Where liquid formulations are contemplated, it is sometimes advisable to add an organic solvent to promote the solubility of certain less polar components, without which the compositions may separate into more than one phase. The addition of the organic solvent may produce a uniform, homogeneous single phase.

Emollients may also be included, especially in lotions to produce a uniform, homogeneous single phase and provide other favorable characteristics. An especially preferred emollient for use in formulations of the present invention is PPG 15-sterol ether which also may be added to the formulations of the present invention for its emulsifying characteristics.

An emulsifying agent or surfactant other than those surfactants, i.e., cationic and nonionic surfactants described hereinabove which are added in certain embodiemtns to stabilize the compositions and reduce the formation of malodorous side products, is often added to embodiments of the present invention to enhance the characteristics of the formulation, to promote the solubility of the protein and other components and the phase stability of the formulation. Such agents also provide detergent-like qualities to the formulations. Suitable surfactants or emulsifying agents may be nonionic, anionic or amphoteric. Of course, one of ordinary skill in the art will recognize that when combinations of surfactants

acteristics to the compositions of the present invention. Suitable thickening agents include polyvinyl pyrollidone, for example PVP K30 (GAF Charlotte, N.C.) polyacrylates, carbomers, for example carboxyvinyl polymer such as Carbapol 940 (available from B.F. Goodrich, Cleveland, Ohio) polyoxyethylene stearyl ethers, for example, polyoxyethylene-2 stearyl ether such as Steareth 2^{tm} (ICI) and polyoxyethylene-20 stearyl ether such as Steareth 20^{tm} (ICI), sodium alginate, carageenan, agar, ethoxylated polyvinyl alcohol, gums, for example methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, propylcellulose and hydroxypropylcellulose, acacia, tragacanth, guar, and quince, among others. In compositions which are contemplated to be formulated as a gel or lotion, Isoseteth 20^{tm} (polyoxyethyleneisohexadecyl ether, ICI), and Steareth 2^{tm} and 20^{tm} are preferred for use as thickening agents. In compositions which are contemplated to be formulated as creams, preferred thickeners include Steareth 2^{tm} and Steareth 20^{tm} and the carbomer polymers, for example Carbapol 940^{tm}.

Preservatives are added for preventing microbial growth in the presence of protein nutrients. Exemplary preservatives include benzoic acid analogs including, among others, sodium benzoate. Other preservatives include propyl and methyl paraben, Dowicil^{tm} (Dow Chemical Corp., Midland, Mi.) and formaldehyde solution. An especially preferred preservative is Germaben II^{tm}, available from Sutton Laboratories, New Jersey.

Other agents may also be added to certain embodiments of the present invention which are intended to treat wounds for the purpose of disinfecting the wounds and surrounding tissue and for providing antimicrobial protection. Among the preferred agents for this use include the topical disinfectants and antiseptics, for example, Benzalkonium chloride, cetrimide, chloramine, chlorhexidine, among others. Antimicrobial agents which may be used in the present invention include neomycin, bacitracin, spectinomycin, sulfa containing preparations, and polymixin, among others, and antifugal agents such as griseofulvin, amphotericin, chlordantoin, clotrimazole, dimethizole, miconazole and nystatin, among others.

Coloring agents and perfume agents may also be added to enhance the characteristics of the formulations.

after or during shampooing, which may only be once or twice a week. The duration of therapy will depend on the condition treated and on the response of the condition to the therapy. Thus, when chronic conditions that do no respond to traditional therapy are being treated, it is to be expected that the duration of therapy will be longer than when less severe conditions are treated.

In producing the compositions of the present invention, a number of methods may be employed. However, a preferred method of producing the compositions involves first activating proteins containing sufficient cysteinyl groups and then stabilizing the activated proteins in the presence of one or more of a reactive zinc salt, a cationic polymer or a surfactant selected from cationic and nonionic surfactants effective to substantially reduce the formation of malodorous side products.

The method involves activating a protein containing cysteinyl groups in the presence of a reducing agent, as described herein, preferably, at a pH above about 9.0 to produce a protein wherein a number of the thiol groups are reduced, i.e., the thiols exist as mercaptides (cysteinyl groups), not dithiols (cystinyl groups). After the activation step, an effective amount of one or more of the reactive zinc salts, cationic polymers and surfactants selected from among cationic and nonion surfactants is combined with the reducing agent, the activated protein and other components. In the case of reactive zinc salts, it has surprisingly been discovered that certain zinc salts, for example ZnO, which are often quite insoluble in water (the solubility of ZnO in water, for example is 0.00016 g/ 100cc) or other carrier used to formulate the compositions of the present invention will dissolve into the water or other carrier to a much greater extent than would otherwise occur in the absence of protein and reducing agent.

Of course, it is also possible to produce the compositions of the present invention by simply mixing the components without regard to timing or activation of the protein component. This method may be useful for producing the compositions of the present invention when the protein is a film-forming protein which contains insufficient cysteinyl groups, i.e., too few cysteinyl groups to covalently bind to the keratinous substrate to produce covalent bonding of protein to

EXAMPLE 1

PHASE	INGREDIENT	PERCENT BY WEIGHT
A.1	DEIONIZED WATER	61.90
B.1	PROPYLENE GLYCOL	0.15
B.2	LANOGEL 41	0.15
B.3	BRIJ 35	0.41
B.4	PVP-K30 (25% SOLN)	0.70
C.1	GLYCERINE	0.50
C.2	CITRIC ACID (5.88% SOLN)	0.14
C.3	HYDROGEN PEROXIDE (3% SOLN)	1.61
C.4	ACETONE	0.41
C.5	ISOPROPANOL (99% SOLN)	1.20
C.6	KERASOL	5.87
D.1	GERMABEN II	2.93
E.1	AMMONIUM THIOGLYCOLLATE (60% SOLN) (previously adjusted to pH=9 with NH3)	10.34
E.2	DEIONIZED WATER	8.55
E.3	KERASOL	2.95
F.1	HAMPENE 100 (EDTA)	0.58
G.1	ZINC OXIDE	1.47
H.2	ZINC SULFOCARBOLATE	0.29
	TOTAL PERCENTAGE	=100.00

PROCEDURE:

In general, all metal (in machinery, containers or otherwise) coming into contact with this formulation at any time must be thoroughly "pickled", i.e. treated with industrial grade nitric acid (about 1N) to avoid any metal oxide effect on the reducing agent during formulation.

1. Heat phase A to 100° F.
2. Combine phase B ingredients separately heating at about 125°F until B.3 is melted. Mix thoroughly, then add to phase A at 100° for 10 minutes.
3. Premix the ingredients in phase C in the order listed while mixing continuously. Add phase C to phases A & B, still at 100°, and mix for 10 minutes.
4. Add phase D to phases ABC while mixing, and mix for another 10 minutes. The batch may become cloudy at this point, but this is normal.
5. Combine the ingredients in phase E in the order listed, and mix for 10 minutes. This step is designed to activate the Kerasol. Add phase E to phases ABCD while mixing and con-

EXAMPLE 3

PHASE	INGREDIENT	PERCENTAGE
A.1	Arlamol E^{tm}	1.36
.2	Brij 72^{tm}	5.21
.3	Mineral Oil 70	11.60
.4	Propylparaben	0.18
B.1	Purified Water	77.4
.2	Disodium EDTA	0.10
.3	Dimethicone^{tm}	0.09
.4	Methylparaben	0.41
.5	Propylene Glycol	1.36
C.1	Dowicil 200^{tm}	0.05
.2	Purified Water	0.50
D.1	Formaldehyde 37%	0.2
E.1	Germaben II^{tm}	0.23

PROCEDURE:

1. Heat A phase components to 70-75°C and mix until uniform.
2. Charge main kettle with water and begin heating to 70-75°C.
3. Add the remainder of phase B components and mix to dissolve the solids.
4. Add, at 70-75°C, A phase to B phase while mixing. Blend well and cool to 35-40°C.
5. Premix C phase and add to the batch when the solution is clear. Add D and E phases one at a time and mix in well.
6. Cool to 25-30°C and use at this temperature.

EXAMPLE 4

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.15
B.1	CARBOPOL 940tm	1.60
C.1	GERMABEN IItm	0.40
D.1	LOTION FROM EXAMPLE 3	8.70
E.1	TRIETHANOLAMINE (99% SOLN)	1.43
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100	0.65
G.2	SCENT	0.87
	TOTAL PERCENTAGE	100.00

EXAMPLE 6

PHASE	INGREDIENT	PERCENTAGE
A.1	Arlamol E™	2.33
.2	Brij 72™	8.93
.3	Brij 78™	2.25
.4	Mineral Oil 70	19.89
.5	Propylparaben	0.31
B.1	Purified Water	62.15
.2	Disodium EDTA	0.16
.3	Dimethicone™	0.16
.4	Methylparaben	0.70
	Propylene Glycol	2.33
C.1	Germaben II™	0.79

Procedure

1. Charge main mixing kettle with B ingredients and heat while mixing to 80-85°C.
2. In a separate container heat A ingredients to 80-85°C and mix until uniform.
3. At 80-85°C, add mixed A ingredients to mixed B ingredients while thoroughly mixing.
4. Cool mixture of A and B to 50-55°C. At 50-55°C, add Germaben (C) and blend in very well. Continue to cool to 30°C and use at this temperature.

EXAMPLE 7

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.30
B.1	CARBOPOL 940™	2.38
C.1	GERMABEN II™	0.59
D.1	LOTION FROM EXAMPLE 6	8.90
E.1	TRIETHANOLAMINE (99% SOLN)	0.25
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100™	0.50
G.2	SCENT	0.88
	TOTAL PERCENTAGE	100.00

EXAMPLE 9

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.35
B.1	CARBOPOL 940^{tm}	1.60 * Acrylic polym
C.1	GERMABEN II^{tm}	0.40
D.1	LOTION FROM EXAMPLE 3	8.70
E.1	TRIETHANOLAMINE (99% SOLN)	1.43
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100^{tm}	0.45
G.2	SCENT	0.87
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. Place phase A in a high speed mixer, create a vortex, sprinkle phase B into vortex, and mix until completely and thoroughly blended.
2. Add phase C to phases AB while mixing, and mix until uniform.
3. Premix phase D. Add phase D to phases ABC, and mix until completely uniform.
4. Add phase E to phases ABCD. This causes the batch to gel.
   Mix until completely uniform.
5. Premix phase F, and add to a separate container sufficient to hold phases F and G.
6. Premix phase G, mix well and allow to stand for 5 minutes.
   Add phase G to phase F and mix mechanically for 10 minutes.
   Keep mixing and add phases FG to phases ABCD while mixing.
   Continue mixing until smooth and uniform.
7. Final pH is about 5.85.

The 8 year old daughter of the above woman, who was prone to hang nails, and consistently had multiple hang nails on each finger, was treated with formulation from example 7. Within 2 days the discomfort of the hang nails disappeared. Within a week there was a marked decrease in the observable hang nails. Within 2 weeks only one hang nail was observable. The mother could not recall when her daughter only had one hang nail.

A boxer dog which had idiosyncratically licked its forepaws since birth 4 years ago was treated with the formulation from Example 10. Previous treatments which utilized antibiotics, steroid hormones, antihistamines, and other foul tasting compositions had all been unsuccessful. Within 30 minutes after the first application, the licking behavior ceased. When treated with this formulation the licking behavior is consistently absent. When it reoccurs, a repeat application effectively stops the licking within 5 minutes.

A 15 month old child with a moderate-severe diaper rash was treated once, overnight, with the formulation from example 7. In the morning the rash was approximately 85% gone. The parents, who had other children, and had suffered similar episodes of diaper rash previously, were amazed at the response.

The invention has been described in such manner as to enable those skilled in the art to understand and practice it, preferred embodiments having been fully identified. It is to be understood, however, that the foregoing examples have been set forth in great detail but should not be viewed as limiting the present invention in any way.

EXAMPLE 24
SCENT REDUCTION

Formulations which did not contain a reactive zinc salt, a cationic polymer or a cationic or nonionic surfactant evidenced a malodor which necessitated considerable scenting with heavy, cloying fragrances. The scents used to cover the malodor were not ideal, because of the heavy fragrance and the need to use high concentrations. Although an improvement over unscented compositions, they were not extremely pleasing and

WHAT IS CLAIMED IS:

1. A composition for treating keratinous tissue in mammals comprising:

a). from about 0.01% to about 25.0% by weight of a film-forming protein;

b). about 0.1 to about 15% by weight of a compatible reducing agent;

c). at least about 0.05 weight percent of a reactive zinc salt; and

d). at least one component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, oxidizing agents, coloring agents, perfuming agents and mixtures, thereof.

2. The composition according to claim 1 wherein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said keratinous tissue.

3. The composition according to claim 2 wherein said reactive zinc salt is selected from the group consisting of zinc oxide, zinc sulfocarbolate and mixtures thereof.

4. The composition according to claim 2 wherein said protein is keratin.

5. The composition according to claim 1 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

6. The composition according to claim 5 wherein said compatible reducing agent is thioglycollic acid or its salt.

7. The composition according to claim 2 wherein said oxidizing agent is selected from the group consisting of sodium perborate, sodium bromate and hydrogen peroxide in an amount ranging from about 0.01 to about 1.5% by weight of said composition.

8. The composition according to claim 1 further comprising an effective amount of a cationic polymer.

9. The composition according to claim 8 wherein said cationic polymer comprises about 0.01% to about 20% by weight of said composition and is a quaternary ammonium containing

salts and mixtures thereof.

21. The composition according to claim 20 wherein said compatible reducing agent is thioglycollic acid or its salt.

22. The composition according to claim 15 further comprising a chelating agent.

23. The composition according to claim 22 wherein said chelating agent is included in amount equal to about 0.05 to about 2.0% by weight of said composition.

24. The composition according to claim 22 wherein said oxidizing agent comprises about 0.01 to about 1.5% by weight of said composition.

25. The composition according to claim 15 wherein said protein is keratin, said reducing agent is ammonium thioglycollate, said zinc salt is a mixture of zinc oxide and zinc sulfocarbolate, said surfactant is a pyrrolidone containing surfactant having an n-octyl group substituted on the nitrogen group of the pyrrolidone and wherein said composition further comprises hydrogen peroxide and ethylenediaminetetraacetic acid.

26. A composition for treating keratinous tissue in mammals comprising:

a). from about 0.01% to about 25.0% by weight of a film-forming protein;

b). about 0.1 to about 15% by weight of a compatible reducing agent;

c). an amount of a cationic polymer effective to substantially reduce the formation of malodorous side products; and

d). at least one component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, coloring agents, oxidizing agents, perfuming agents and mixtures thereof.

27. The composition according to claim 26 wherein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said tissue.

28. The composition according to claim 26 wherein said cationic polymer is a quaternary ammonium containing polymer comprising at least about 0.01 weight percent of said composition.

36. The composition according to claim 35 wherein said surfactant comprises about 0.05% to about 15% by weight of said composition.

37. The composition according to claim 35 wherein said surfactant is a nonionic pyrrolidone containing surfactant substituted on the nitrogen of the pyrrolidone ring with a hydrophobic group selected from the group consisting of n-octyl, dodecyl and coco and tallow alkyl groups.

38. The composition according to claim 35 wherein said film-forming protein component is keratin.

39. The composition according to claim 35 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

40. The composition according to claim 39 wherein said compatible reducing agent is thioglycollic acid or its salt.

41. The composition according to claim 39 wherein said oxidizing agent is selected from the group consisting of sodium perborate, sodium bromate and hydrogen peroxide and comprises about 0.01 to about 1.5% by weight of said composition.

42. A method of treating normal and abnormal keratinous tissue to improve its condition, appearance, strength and promote its growth by contacting the tissue with any of the compositions from claims 1 through 41.

43. A method for treating conditions of keratinous tissue in mammals including wounds, abrasions, pressure sores, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, sebborhea, psoriasis, acne, acne scars, itching, callouses, corns, burns, miscellaneous rashes, non-specific dermatitis, eczematoid dermatitis, wrinkles, hang nails, chronic dermatitis, equine exuberant granuloma, decubitis ulcers, and canine cutaneous granulomas comprising applying to the effected area of the skin a composition comprising any of the compositions from claims 1 through 41.

44. A method for producing a composition for treating keratinous tissue comprising:

a. exposing a cysteinyl containing protein comprising

said film-forming protein is keratin.

52. The composition according to claim 48 wherein said reducing agent is thioglycollic acid or a salt of thioglycollic acid.

53. The composition according to claim 52 wherein said reducing agent comprises at least about 0.5 to about 10% by weight of said composition.

54. A method of cosmetically treating the affects of aging skin in mammals including wrinkles or promoting hair growth, nail growth and in stabilizing hair loss comprising applying any of the compositions from claims 1-41 to the skin or scalp of a subject to decrease wrinkles, decrease hair loss and promote hair growth.